Armed Forces College of Medicine

AFCM

Neuroscience Module

Lecture (8)

Neurological disorders related to amino acids metabolism (2)

By

Enas Samir Nabih

Professor of Medical Biochemistry and Molecular Biology

Key points

The biochemical basis of albinism, phenylketonuria and alkaptonuria

INTENDED LEARNING OBJECTIVES (ILO)

By the end of this lecture the student will be able to:

1. Identify the metabolic defects in phenylketonuria, alkaptonuria and albinism

The metabolic disorders related to defects in amino acids metabolism

- **Glycine:** glycinuria, and primary hyperoxaluria (refer to metabolic pathways of the kidney).
- **Cysteine:** Cystinuria, Cystinosis (refer to metabolic pathways of the kidney) and Homocystinuria.
- **Branched chain amino acids:** maple syrup urine disease.
- **Tryptophan:** hartnup disease (refer to metabolic pathways of the kidney) and pellagra.
- **Phenylalanine and tyrosine:** albinism, phenylketonuria and alkaptonuria.

Case study

A female child was detected to have a phenylketonuria at the age of one year and seven months.

She was born of consanguineous marriage.

She was referred for mild delay in his milestones.

She was only on breast feed for first four months of life. Light colored hair was noticed at the age of 4 months.

Her urine has "musty odor".

Metabolic disorder of phenylalanine

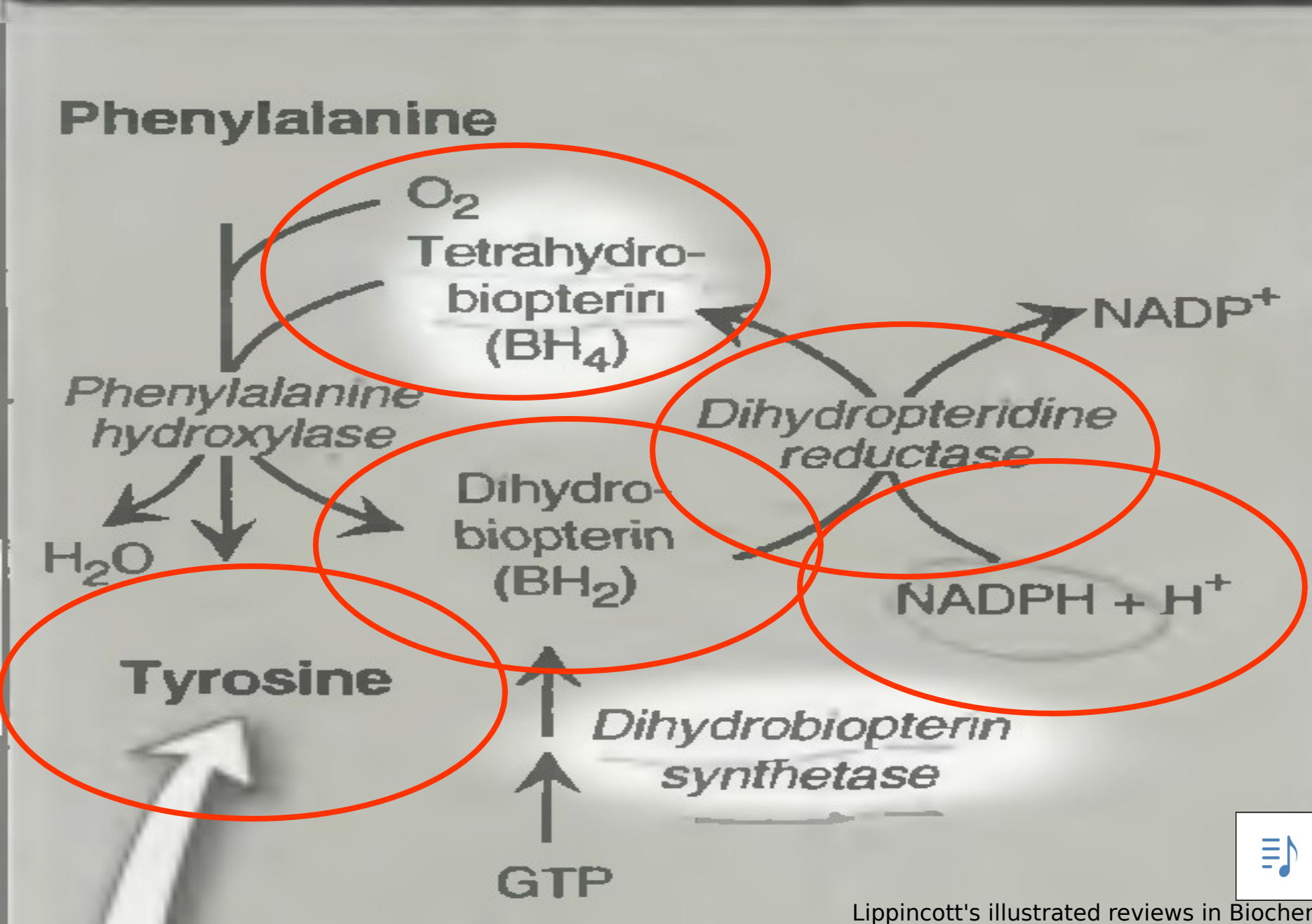
(phenylketonuria)

Phenylalanine and tyrosine

- **Phenylalanine is essential AA.**

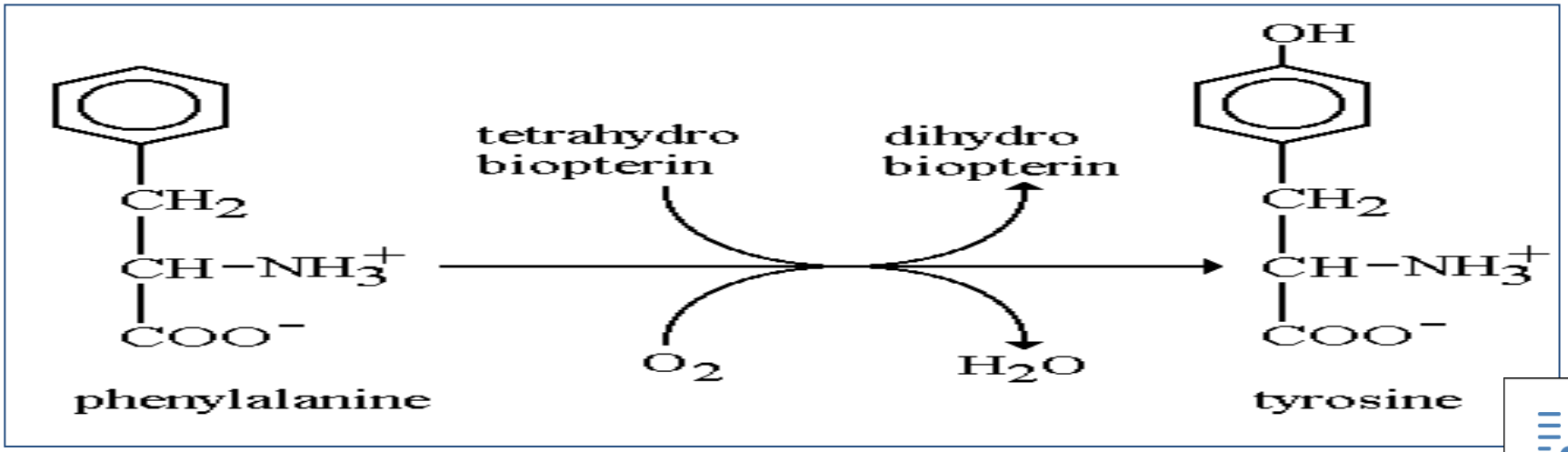
- **Tyrosine is non essential (synthesized from phenylalanine).**

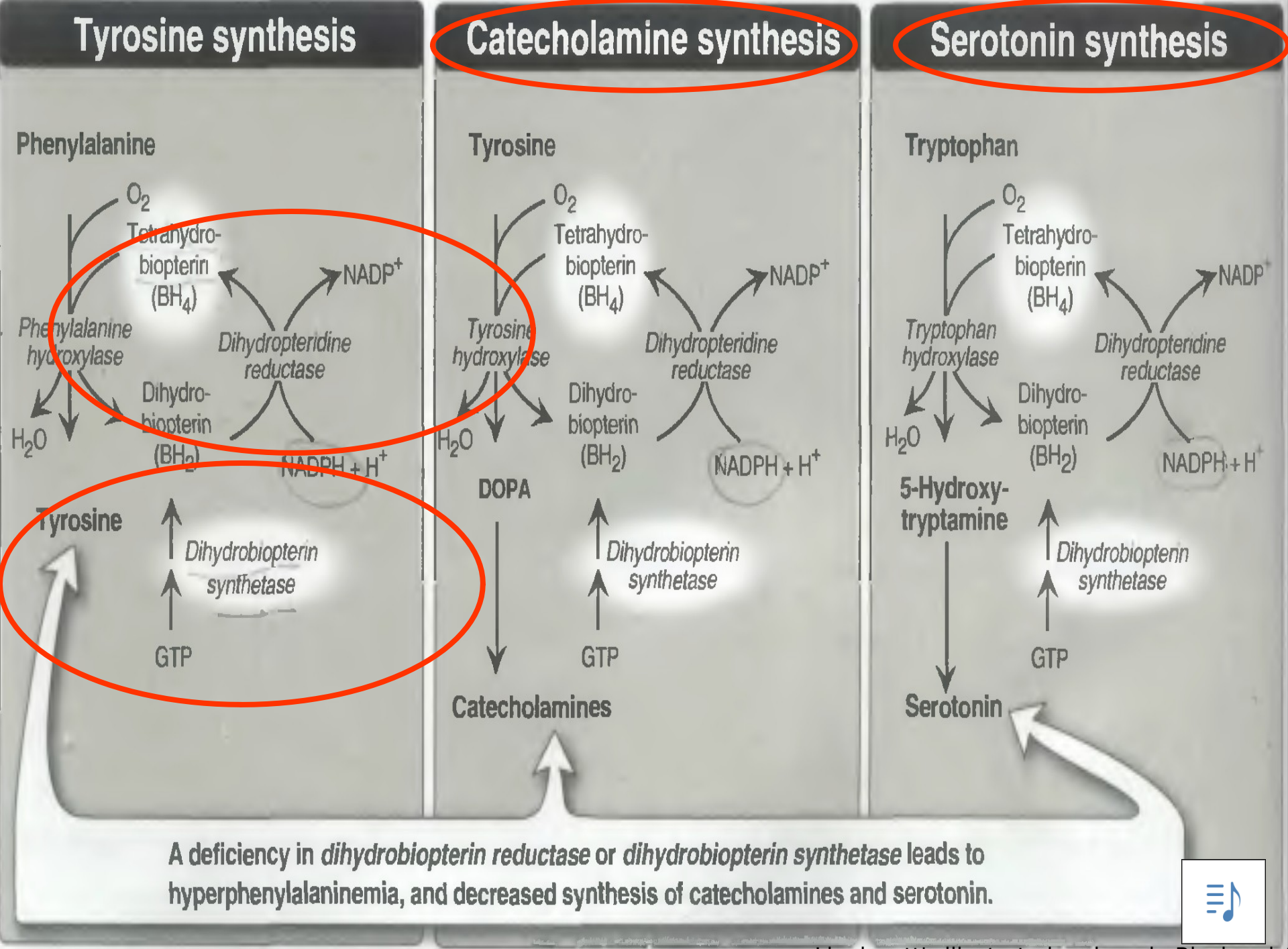
Tyrosine synthesis



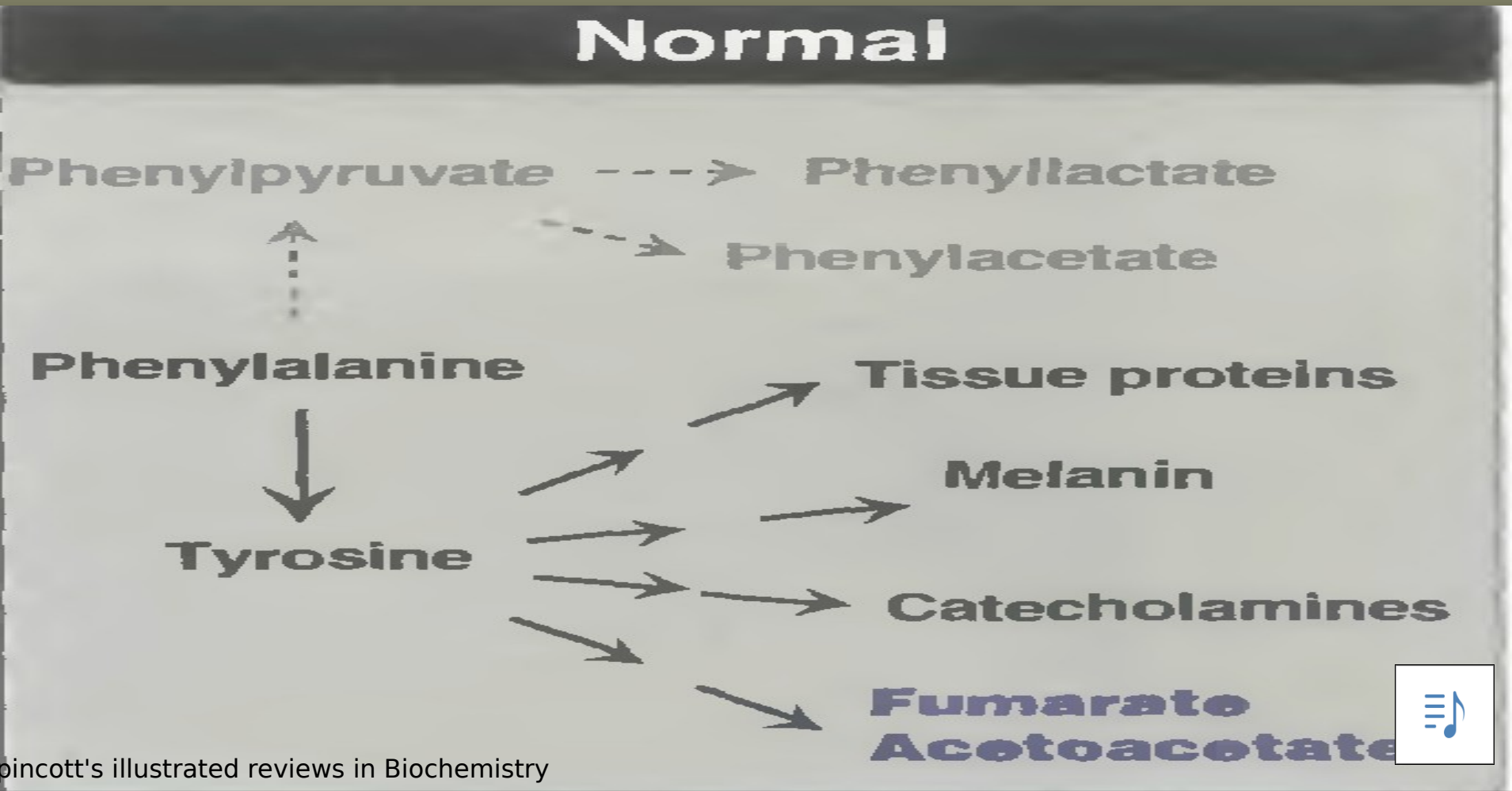
Phenylketonuria

is a metabolic disorder caused by either a deficiency of the enzyme phenylalanine hydroxylase or the enzymes that synthesize or regenerate the coenzyme tetrahydrobiopterin



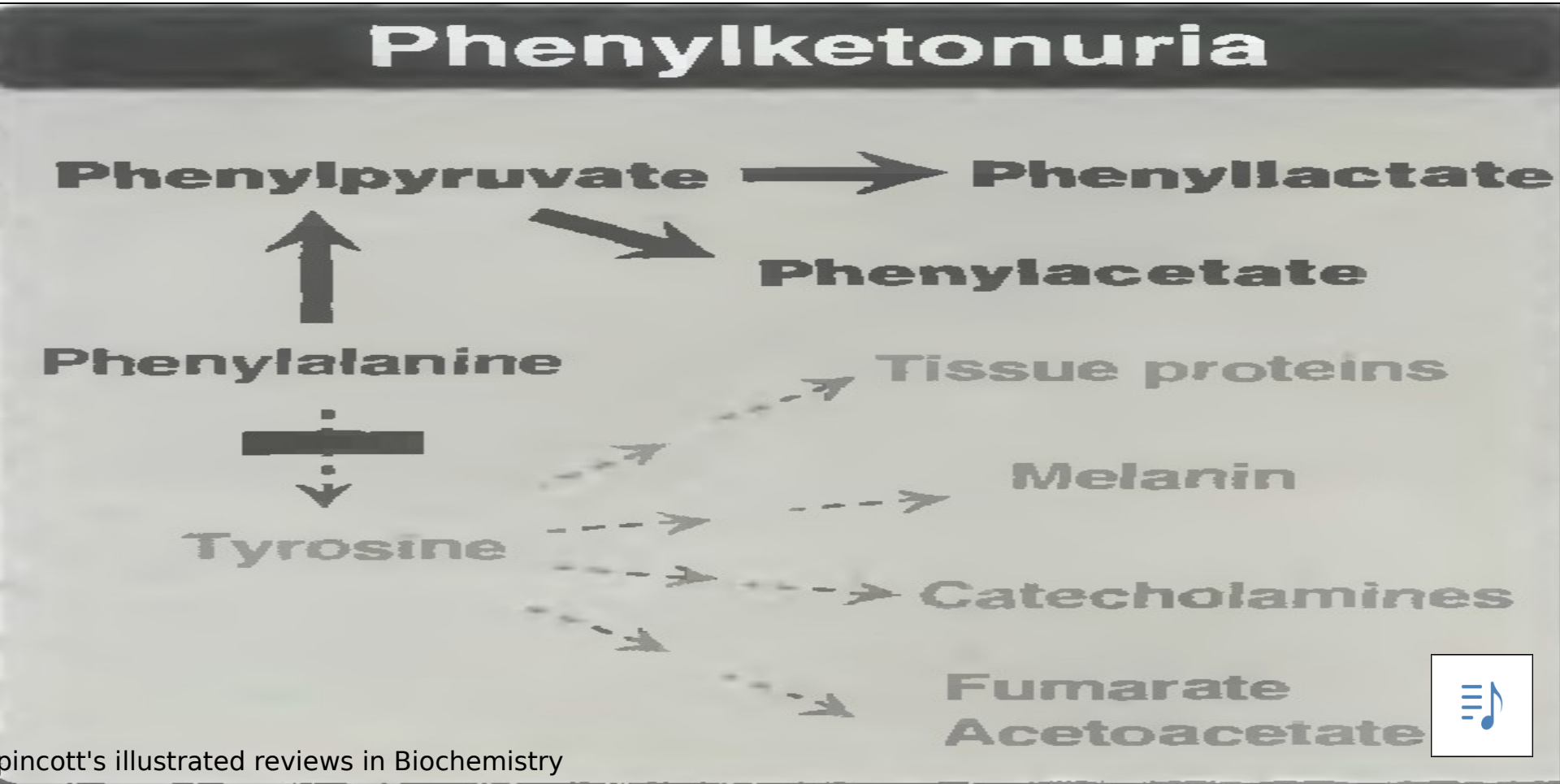

Tyrosine synthesis
Catecholamine synthesis
Serotonin synthesis
Phenylalanine
Tyrosine
Tryptophan
O_2
Tetrahydrobiopterin (BH_4)
$NADP^+$
Phenylalanine hydroxylase
Tyrosine hydroxylase
Tryptophan hydroxylase
Dihydropteridine reductase
Dihydrobiopterin (BH_2)
H_2O
$NADPH + H^+$
Tyrosine
DOPA
5-Hydroxytryptamine
Dihydrobiopterin synthetase
GTP
Catecholamines
Serotonin
A deficiency in dihydrobiopterin reductase or dihydrobiopterin synthetase leads to hyperphenylalaninemia, and decreased synthesis of catecholamines and serotonin.

Phenylalanine



pincott's illustrated reviews in Biochemistry

Phenylketonuria



pincott's illustrated reviews in Biochemistry

Clinical picture:

1) CNS symptoms:

- **Severe intellectual delay (mental retardation) due to deficiency of brain catecholamines and accumulation of toxic products in tissues.**
- **These toxic products are derived from abnormal metabolism of phenylalanine.**

- **2) Depigmentation:**
- **due to↓ melanin synthesis.**

- **3) Urine: bad mousy (musty) odor caused by abnormal metabolites.**

Treatment:

- The goal of treatment is to keep plasma phenylalanine levels within the normal range through diet.

- a- Phenylalanine low diet.
- b- Supplements of Tyrosine in diet.

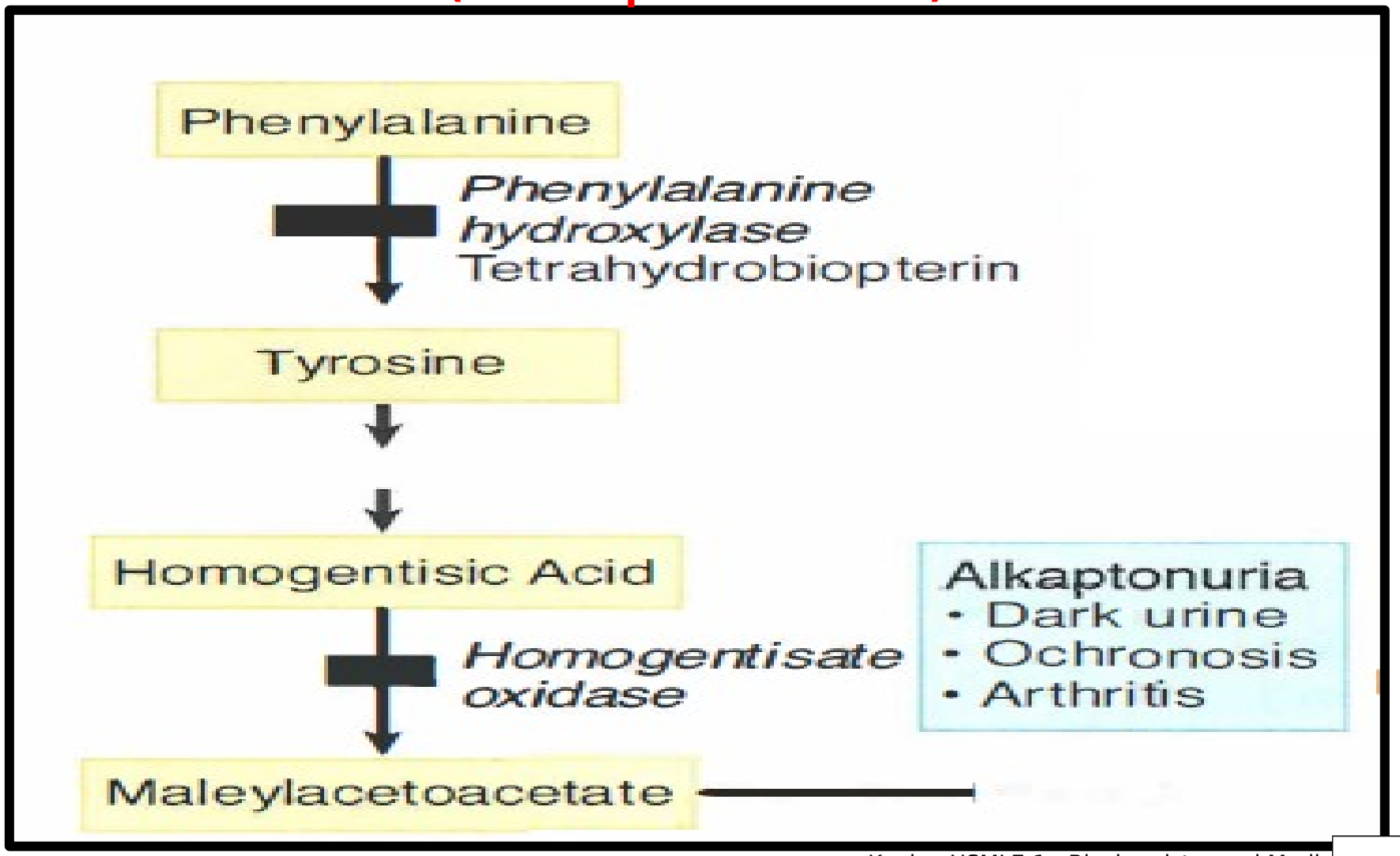
The biochemical basis of albinism, phenylketonuria and alkaptonuria (Quiz)

Explain the biochemical basis of phenylketonuria

Homogentisate Oxidase Deficiency (Alkaptonuria)

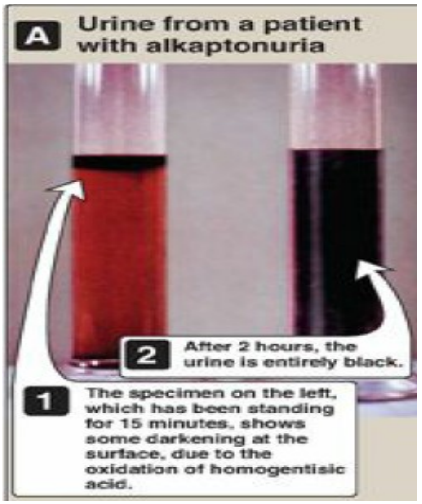
- is a rare metabolic condition involving a deficiency in homogentisic acid oxidase, resulting in the accumulation of homogentisic acid (HA), an intermediate in the degradative pathway of tyrosine

Homogentisate Oxidase Deficiency (Alkaptonuria)

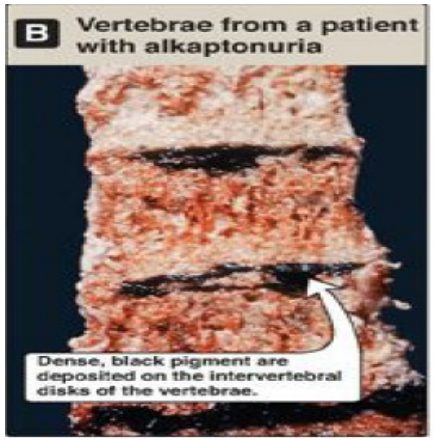


Symptoms

- Homogentisic aciduria (the urine contains elevated levels of HA, which is oxidized to a dark pigment on standing
- Arthritis
- Deposition of black pigment (ochronosis) in cartilage and collagenous tissue


A
Urine from a patient with alkaptonuria
2
After 2 hours, the urine is entirely black.
1
The specimen on the left, which has been standing for 15 minutes, shows some darkening at the surface, due to the oxidation of homogentisic acid.

Lippincott's illustrated reviews biochemistry


B
Vertebrae from a patient with alkaptonuria
Dense, black pigment are deposited on the intervertebral disks of the vertebrae.

Lippincott's illustrated reviews biochemistry

The biochemical basis of albinism, phenylketonuria and alkaptonuria (Quiz)

Explain the biochemical basis of alkaptonuria

Albinism

Definition:

is a congenital disorder characterized in humans by the complete or partial absence of pigment in the skin, hair and eyes.

https://www.google.com/search?q=albinism&hl=en-US&source=lnms&tbm=isch&sa=X&ved=0ahUKEwjJgvHM1onkAhWOCuwKHRunAIcQ_AUIESgB&biw=1366&bih=662

Albinism

1-Deficiency of tyrosinase in melanocytes

2- Cu+2 deficiency→↓activity of tyrosinase enzyme→depigmentation .

https://www.google.com/search?q=albinism&hl=en-US&source=lnms&tbm=isch&sa=X&ved=0ahUKEwjJgvHM1onkAhWOCuwKHRunAIcQ_AUIESgB&biw=1366&bih=662

Clinical picture

1) **vision defects: photophobia, nystagmus, and amblyopia.**

2) **Lack of skin pigmentation makes for more susceptibility to sunburn and skin cancers.**

Lecture Quiz

The diet of a child suffering from maple syrup urine disease should be low in:

a) Phenylalanine

b) Methionine

c) Tryptophan

d) Branched chain amino acids

e) Cysteine

Summary

- Phenylketonuria (PKU) is an inborn error of metabolism that results in decreased metabolism of the amino acid phenylalanine. Untreated, PKU can lead to intellectual disability, seizures, behavioral problems, and mental disorders. It may also result in a musty smell and lighter skin.
- Alkaptonuria is a rare genetic metabolic disorder characterized by the accumulation of homogentisic acid in the body. Affected individuals lack enough functional levels of an enzyme required to breakdown homogentisic acid. Affected individuals may have dark urine or urine that turns black when exposed to air.
- Albinism is a congenital disorder characterized in humans by the complete or partial absence of pigment in the skin, hair and eyes. Albinism is associated with a number of vision defects, such as photophobia, nystagmus, and amblyopia. Lack of skin pigmentation makes for more susceptibility to sunburn and skin cancers.

SUGGESTED TEXTBOOKS

- Lippincott's illustrated reviews in Biochemistry
- Kaplan USMLE-1 - Biochemistry and Medical Genetics

THANK YOU